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Understanding the regioselectivity in Scholl reactions for the synthesis of oligoarenes[†]

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A short reaction sequence leads to oligoarene derivatives utilising a regioselective Scholl reaction for the unprecedented cyclisation to the mono-functionalised oligoarene under methanol elimination. Quantum-chemical investigations reveal the reason for the remarkably high regioselectivity.

The Scholl reaction is the oxidative cyclisation of suitable terphenyl and higher open oligoaryl derivatives (such as **3**) for the formation of triphenylenes and other cyclised oligoarene products (*e.g.* **4**, **5**).¹ For this purpose a range of oxidizing agents can be applied successfully and out of many reagents iron trichloride is the most prominent.² Recent applications describe the use of hypervalent iodine derivatives introduced by Kita *et al.*³ and the combination of $MoCl_5/TiCl_4$ introduced by Waldvogel *et al.*⁴ for moderately activated starting materials. Contemplating the literature it becomes obvious that for the synthesis of oligoarene derivatives generally symmetrical starting materials are used.

Inspired by the work of King *et al.*⁵ who investigated the applicability of the Scholl reaction and determining the scope and limitations of unsymmetrical starting materials, *Müllen* and our group independently noticed an unprecedented high selectivity in a Scholl reaction leading to tribenzo[*fg,ij,rst*]pentaphene derivatives such as **4** (Scheme 1).^{6,7}

The synthesis of **3** was accomplished in three steps utilizing a cobalt-catalysed Diels–Alder reaction of **1** with **2** in the key step.⁸ From **3** the Scholl reaction with FeCl₃ as oxidizing agent generates regio-isomer **4** exclusively while the alternative regioisomer **5** was not observed.⁸ Intrigued by Müllen's statement "*The factors controlling this reaction are still undetermined*."⁶ we decided to investigate this selectivity in more detail. For this purpose, **6a/b** were synthesised in order to force the reaction towards the regioisomers **7** by blocking positions with alkyl and other functional groups (Scheme 2).

When a methyl or an isopropyl group were selected as functional groups for blocking coupling sites in **6**, the oxidation with FeCl₃ led to the formation of various products.⁹ This finding is interesting since it illustrates that the alkyl groups of



Scheme 1 Regioselective synthesis of oligoarene 4.



Scheme 2 Attempted synthesis of oligoarenes of type 7.

the central arene moiety are non-innocent substituents while the alkyl chains in the vicinity of the molecule remain unchanged. The oxidation of this particular central benzene ring leads to the formation of benzylic radicals initiating side reactions. This agrees with the electrochemical oxidation of toluene and multiple methylated benzene derivatives leading to a variety of products by arene–arene coupling as well as arene–side chain and side chain–side chain coupling reactions.¹⁰ On the other hand, when the functional group is a methoxy group (FG = OCH₃ in 6), the transformations of 6 with FeCl₃ led to 8a (FG = OCH₃) as the major product in 74% yield with loss of a methoxy group. Unexpectedly, the anticipated product of type 7 was not formed. In addition, when fluorine was chosen as a functional group product 8b (FG = F) was formed exclusively in 55% yield

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Scheme 3 Proposed reaction pathway for the formation of **8a** by a Scholl reaction including the elimination of methanol.

(73% based on recovered starting material). Although oxidation of the fluoro-substituted starting material **6b** was significantly slower, compound **7** could also not be isolated. To exclude that FeCl₃ acts as Lewis acid being responsible for the elimination of methanol, the reaction with **6a** was performed with DDQ (2,3-dichloro-5, 6-dicyanobenzo-quinone) as oxidant. The result was identical to the reaction with FeCl₃ leading to product **8a** in 76% yield. Repeating the reaction with MoCl₅/TiCl₄ and adopting a procedure by Waldvogel led to the desired product **8a** in 61%.¹¹

The formation of products of type **8** can be rationalized by a radical cation initiated electrocyclic ring closure (indicated by the bold highlighted double bonds in **9a**, Scheme 3) to generate intermediates such as **10a** which can eliminate methanol (or HF) for the formation of the detected ring systems (**8**).¹² After elimination of MeOH from **10a** the obtained radical cation undergoes two more electrocyclic ring closure/oxidation reactions (in total $-3e^-$, $-4H^+$) for the synthesis of **8a**.

At this point it was not clear whether the electrocyclic reaction involving the methoxy position took place during the first ring closure process or if the second electrocyclic ring closure incorporates the step to eliminate methanol.

For this purpose test system **11** (Scheme 4) was synthesized where the Scholl reaction led to two products. Following pathway **b** product **14** was isolated in 8% yield *via* **12** while the major product **14**' was formed by dimerization of **12** in 51% yield. Utilising DDQ¹²⁻¹⁴ as oxidant the dimer **14**' was isolated in 39% yield accompanied with 20% of recovered starting material, whereas **14** was formed in very low yield (<5%).¹⁵

The alternative product 13 which is possibly formed *via* pathway **a** was not detected. The results indicate that the reaction *via* pathway **b** is strongly favoured over reaction pathway **a** when FeCl₃ or DDQ were used as oxidant.

For the first system described herein, the Scholl reaction of **3** and the regioselective formation of **4**, these results are rather irrelevant because the regioselectivity for the product formation



Scheme 5 Radical cation intermediate 15 for the selective formation of 4. The dotted lines indicate the positions for carbon–carbon bond formation.



Scheme 6 Possible reaction pathways toward 8a. The dotted lines indicate the positions for carbon–carbon bond formation.

is determined in the second step of the reaction and not in the first cyclisation step (Scheme 5).

In this case the reaction pathway **c** is exclusively chosen over pathway **d** in the proposed intermediate **15** leading to product **4**. In the cases of the functionalised starting materials **6a** and **6b** two different scenarios have to be taken into account (Scheme 6).

The control experiments outlined in Scheme 4 revealed that intermediate 16 is not formed so that the two reaction pathways e and f can be ignored. Intermediate 17 is formed by the "nonclassical" cyclisation under Scholl conditions. From there, only pathway g is chosen for the formation of product 8a over pathway h, which would lead to a doubly demethoxylated product, which is not observed.

Quantum-chemical calculations at the DFT level (B3LYP/ def2-TZVPP//LC- ω PBE/def2-SVP) were undertaken to explain the observed regioselectivity. The starting points for the calculations were the radical cations of **15** and **17** (with hexyl-groups substituted by methyl-groups) which have been termed **A**_X with X = H, F, OMe (see Fig. 1). Since the biphenyl-moiety was found to exhibit only a small difference between rotamers ($\Delta E < 5$ kcal mol⁻¹) of the C–C bond to the central ring, the conformation of **A**_X is not relevant.

Transition structures and intermediates were located for both possible pathways proposed in Schemes 5 and 6.¹⁶ The relative energies of the transition states indicate that the



Scheme 4 System **11** for testing the site-specific Scholl reaction. The dotted lines indicate the positions for carbon–carbon bond formation.



Fig. 1 Free energies $\Delta G(\text{LC-}\omega\text{PBE}/\text{def2-SVP})$ for the selectivitydetermining transition states relative to $\mathbf{A}_{\mathbf{X}}$ (X = H, F, OMe (underlined values); R = Me).

Table 1 Energy differences (kcal mol^{-1}), bond lengths for the newly formed bond (Å) and transition state frequencies (cm^{-1}) for the crucial transition states shown in Fig. 2

				TSA-B1 _x		TSA-B2 _X	
X	$\Delta E^{a,b}$	$\Delta E^{a,c}$	$\Delta G^{a,b}$	<i>r</i> (C–C)	ν_{TS}	<i>r</i> (C–C)	ν_{TS}
H	2.8	0.7	2.0	1.781	-495	1.798	-589
F	4.8	2.6	4.2	1.729	-497	1.772	-531
OMe	6.1	5.3	5.3	1.775	-488	1.771	-523
^{<i>a</i>} (Free	e) energ	y diffe	rence:	E/G(TSA-E	31 _x) –	E/G(TSA	A-B2_X).
^{<i>b</i>} LC-0	oPBE/def	2-SVP.	B3LYP	/def2-TZV)	PP//LC-α	oPBE/def2	-SVP.

barriers towards the experimentally observed product $D1_X$ (*via* radical cation $C1_X$) are favoured for all substituents X.

The free energy differences $G(TSA-B1_x) - G(TSA-B2_x)$ are 2.0 kcal mol⁻¹ (X = H), 4.2 kcal mol⁻¹ (X = F) and 5.3 kcal mol⁻¹ (X = OMe) which are in line with the experimentally observed high regioselectivity of the Scholl reaction. Note that the calculated transition states exhibit antarafacial arrangements of the aromatic rings. An alternative suprafacial arrangement possesses transition states which are 5–10 kcal mol⁻¹ higher in energy. Therefore, they are not further discussed (details can be found in the ESI†).

The calculations indicate that the transition states lead to energetically high lying intermediates $B1_x$ and $B2_x$ for all substituents. We conclude that the intermediates are instantaneously deprotonated by chloride anions which are available in solution forming HCl. Indeed, HCl has been experimentally observed, confirming this assumption. The final product regioisomer $D1_x$ is then formed *via* radical cation $C1_x$ in a third electrocyclic reaction, in accordance with the experiment. The energy differences for the crucial transition states are consistent for both density functionals applied and range between 0.8 and 6.1 kcal mol⁻¹ (Table 1). The same holds true for the difference in free energies. Thus for all substituents a clear kinetic preference for the experimentally observed pathway is found.

In the analysis of the crucial transition states we found that the preference for the pathway *via* **TSA-B1**_x can be understood in terms of frontier orbital analysis. Fig. 2 shows the LUMO of A_H and A_F (A_{OMe} looks similar). Upon inspection of the orbital coefficients it can be seen that the coefficients at the central aromatic ring are distributed unevenly. For all substitution patterns, the carbon atoms being attacked through pathway c (Scheme 5, A_H) or g (Scheme 6, A_F) exhibit the larger orbital coefficients.

It follows that the observed reactivity pattern is in line with an orbital controlled reaction which may be used as an easy probe for future studies on regioselective Scholl reactions.



Fig. 2 Lowest unoccupied orbital (LUMO) for A_H (left) and A_F (right) with orbital energies (B3LYP/def2-TZVPP).

In conclusion, we presented a comprehensive explanation for the highly regioselective Scholl reaction leading to the formation of tribenzo[*fg,ij,rst*]pentaphene derivatives by joint experimental and quantum chemical investigations. Also, the successful isolation of unprecedented mono-functionalised tribenzo-[*fg,ij,rst*]pentaphene derivatives will be useful to evaluate future syntheses of oligoarene and graphene materials *via* a Scholl reaction for unsymmetrical starting materials in the synthesis of complex polyarene architectures.

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- 15 The product was accompanied by an unidentified side-product. 16 Note that the transition states $TSA-B1_x$ could only be located with
- the functional LC- ω PBE. Previous attempts with B3LYP, BP86, M06-2X, B97D and TPSS failed to locate a stationary point. The observation that the identification of intermediates depends on the method employed in radical cation reactions has been found earlier (see ref. 13). Extensive benchmark studies on present day density functionals (L. Goerigk and S. Grimme, Phys. Chem. Chem. Phys., 2011, 13, 6670) reveal that care has to be taken in choosing the right functional and basis set for studies in organic chemistry similar to more challenging transition-metal catalyzed reactions. Although for pericyclic reactions B3LYP has been found to provide reasonably accurate results (T. Schwabe and S. Grimme, Acc. Chem. Res., 2008, 41, 569) excellent agreement with higher level calculations has been found for radical cation reactions. (U. Haberl, O. Wiest and E. Steckhan, J. Am. Chem. Soc., 1999, 121, 6730.) For further details see the ESI.[†] In accordance with earlier observations (ref. 13 and therein), a non-aromatic to slightly antiaromatic character of the transition states has been found by NICS computations.